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Assessment of Surgical sTaging versus Endobronchial and endoscopic ultrasound in lung cancer: a Randomised controlled trial (ASTER)

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1. Summary

Background:

Lung cancer is the second most common cause of cancer in the UK and has a very high mortality rate. Both treatment and prognosis depend upon stage at presentation. Mediastinal staging is a field that is rapidly developing. Staging by FDG-PET has dramatically reduced the rate of futile thoracotomies. EUS-FNA and EBUS-TBNA are two complementary ultrasound guided biopsy techniques which together allow access to almost all mediastinal lymph nodes (LN): for EUS-FNA: 4L, 7, 8L/R, 9L/R and for EBUS-TBNA: 2R/L, 4R/L, 7. This means that the combination of both techniques allows a comprehensive (bilateral N2 and N3) mediastinal examination (with the exception of the para-aortic stations 5 and 6). Non-randomized case series have indicated the potential of EUS-FNA and EBUS-TBNA for mediastinal staging. However, these techniques have not been validated against the current 'gold standard' of care which is surgical staging in a prospective randomised controlled fashion.

Hypothesis: The null hypothesis is that there is no difference between sensitivity, diagnostic accuracy and negative predictive value of endobronchial with endoscopic ultrasound guided biopsy of lymph nodes and surgical staging.

Patients: Patients with (suspected) NSCLC who are judged to be candidates for surgical resection but in whom malignant N2/N3 lymph node involvement is suspected based on clinical staging (including chest X-ray, CT thorax, FDG-PET or integrated FDG-PET/CT) are eligible for this study. A cytological or histological diagnosis of lung cancer is not required at the time of randomisation. Patients with proven distant metastases (M1) are excluded from this study.

Study design: A prospective randomised controlled multi-center double arm diagnostic phase III trial in which patients are randomly assigned to either surgical staging (arm B) or echo-endoscopic staging with both EUS-FNA and EBUS-TBNA (arm A). EUS-FNA and EBUS-TBNA are performed in one session. Surgical staging is defined as cervical mediastinoscopy, anterior (parasternal) mediastinotomy, thoracoscopic mediastinal exploration or any combination.

EUS-FNA/EBUS-TBNA will be considered positive if one or both of the diagnostic procedures yield tissue proof of mediastinal metastases (N2/N3).

In arm A (study arm), if no N2 or N3 lymph node metastases are found by either EUS-FNA or EBUS-TBNA patients will subsequently be offered a confirmatory surgical staging procedure prior to proceeding to a thoracotomy with systematic lymph node dissection.

Objectives:

Primary objective

The primary research objective of the study is to determine whether EBUS-TBNA combined with EUS-FNA is better than standard surgical staging techniques in terms of sensitivity, diagnostic accuracy and negative predictive value for diagnosing and staging the mediastinum in lung cancer.

Secondary objectives are

- Determination of the sensitivity and accuracy of EBUS and EUS compared with surgical staging for determining mediastinal tumour invasion (T4).
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- A comparative cost analysis of the diagnostic strategies of the two trial arms.
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- Assessment of the complication rates in each arm
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  An estimation of the saving of surgical staging procedures that might be possible in the future if EBUS-TBNA/EUS-FNA is shown to have greater sensitivity and diagnostic accuracy and becomes the new 'gold standard' staging procedure.

- Estimation of how many futile thoracotomies can be avoided by performing EBUS-TBNA and EUS-FNA rather than surgical staging procedures
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Assessment of inter-observer variability of cytopathological evaluation of EBUS-TBNA and EUS-FNA samples

Statistical analysis:

In the sample size calculation the following assumptions were made:

The prevalence of mediastinal nodal disease in patients with lung cancer is 70%. The sensitivity of mediastinoscopy to detect mediastinal nodal involvement is 70%. The sensitivity of EUS-FNA and EBUS-TBNA for detection of mediastinal nodal involvement is 90%.

Using standard calculation techniques, the sample size required is (2 x 71 in each arm) with a power of $1-\beta = 0.8$, type 1 error $\alpha = 0.05$ and two sided testing. Assuming 5% incomplete CRFs and assuming that only 70% of patients will have mediastinal disease the total sample size becomes 214 patients.

2. Introduction

- 2.1 Background

Lung cancer is the second most common cancer in England and Wales and is the most common cause of cancer death. Non small cell lung cancer (NSCLC) accounts for 80% of all cases. The overall five survival is approximately 10% [1]. Treatment of lung cancer is influenced by stage. Accurate staging is therefore important in order to optimise treatment regimens. The incorporation of positron emission tomography (PET) into staging algorithms has considerably reduced the number of futile thoracotomies [2]. PET/CT is more accurate than computed tomography (CT) in detecting mediastinal lymph node metastases, with a negative predictive value of 93-95%. However, a positive predictive value of 74-90% makes pathological verification of mediastinal hotspots necessary in order to avoid patients being denied possible curative surgery [3-5].

The current standard of care requires surgical staging of enlarged and/or FDG-PET/CT avid mediastinal lymph nodes by a surgical staging procedure such as mediastinoscopy, mediastinotomy or thoracoscopic mediastinal exploration [6]. However, these techniques are invasive and require general anaesthesia and hospitalisation. In addition, the accuracy of these procedures is variable and ranges between 80-90% [6;7]. Although the specificity is 100%, the sensitivity is lower and ranges between 66% [8] and 75-90 % [6]. The accuracy of mediastinoscopy to stage lung cancer is therefore mainly determined by the high specificity while there is room to improve the sensitivity and the negative predictive value.

Endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) and more recently endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) are two minimally invasive diagnostic techniques that allow real-time controlled punctures of mediastinal lymph nodes [8-16]. These techniques are performed in an outpatient setting under conscious sedation. Non-randomized trials in selected patient populations have suggested that these techniques can obviate the need for surgical staging procedures in up to 70% of the cases [9 17]. EUS-FNA and EBUS-TBNA are complementary techniques with EUS allowing access to mediastinal lymph node groups 4L, 7, 8L/R, 9L/R and EBUS giving

access to mediastinal lymph node stations 2R/L, 4R/L, 7, [18 13]. This means that the combination of both techniques enables a complete (bilateral) mediastinal examination. With EBUS-TBNA hilar and intrapulmonary nodal stations 10R/L, 11R/L can also be assessed. In addition, in selected cases echoendoscopy offers the possibility to assess whether a tumour is invading the mediastinum (T4) [8]. In previous studies we have reported the value of adding EUS-FNA to mediastinoscopy regarding mediastinal staging [8] and the impact of EUS-FNA on the prevention of surgical staging [9;12].

Data regarding combined echo-endoscopic staging (EUS-FNA combined with EBUS-TBNA) compared with surgical staging for evaluation of mediastinal lymph nodes are currently not available.

- 2.2 Rationale for this study

Current international guidelines for the staging of NSCLC advocate staging by mediastinoscopy when locally advanced disease is suspected [6;19;7;20]. Locally advanced disease is defined as either N2 or N3 or T4. Mediastinoscopy has limitations in its diagnostic reach to access some mediastinal nodes, is expensive and requires an in-patient stay. Recent reports suggest that complete accurate loco-regional staging can be assessed by the combination of EUS-FNA and EBUS-TBNA in an ambulatory setting. (Villman ref 18, Wallace, World EUS / DDW 2006). If this holds true, improved, less invasive and more cost effective care can be provided for this large group of patients.

3. Study Objectives

- 3.1 Primary objectives

  The primary research objective of the study is to determine whether EBUS-TBNA combined with EUS-FNA is better than standard surgical staging techniques in terms of sensitivity, diagnostic accuracy and negative predictive value for diagnosing and staging the mediastinum in lung cancer.

  The null hypothesis is that there is no difference between sensitivity, diagnostic accuracy and negative predictive value of EBUS-TBNA combined with EUS-FNA and surgical staging.

- 3.2 Secondary objectives
  - Determination of the sensitivity and accuracy of EBUS and EUS compared with surgical staging for determining mediastinal tumour invasion (T4).
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  - A comparative cost analysis of the diagnostic strategies of the two trial arms.
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  - Assessment of the complication rates in each arm.
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    An estimation of the saving of surgical staging procedures that might be possible in the future if EBUS-TBNA/EUS-FNA is shown to have greater sensitivity and diagnostic accuracy and becomes the new 'gold standard' staging procedure.

  - Estimation of how many futile thoracotomies can be avoided by performing EBUS-TBNA and EUS-FNA rather than surgical staging procedures.
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  - Assessment of inter-observer variability of cytopathological evaluation of EBUS-TBNA and EUS-FNA samples

4. Study plan and procedures

- 4.1 Overall study design

This is a prospective international multi-centre open randomized controlled phase III study.

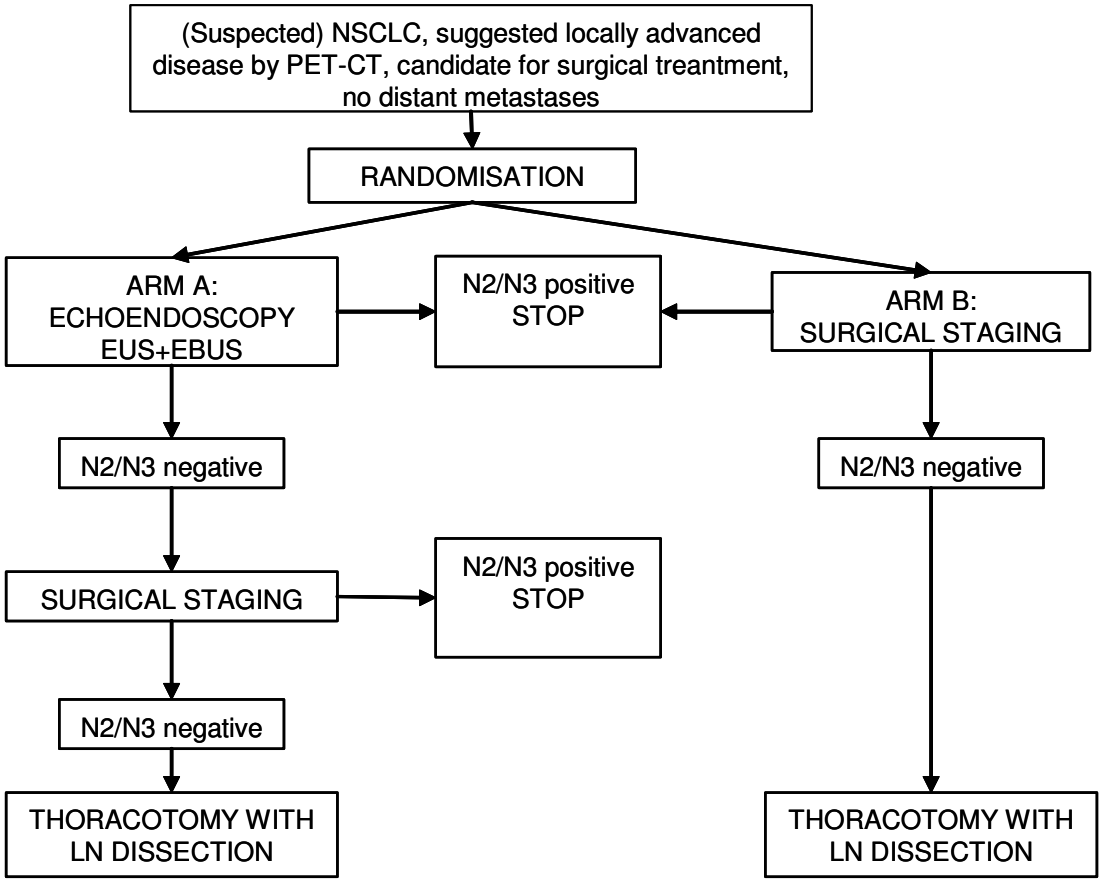
- 4.2 Clinical Work-up (CWU)

Patients are evaluated by history, physical examination, full blood count, renal and liver function tests, chest X-ray, bronchoscopy, CT of the chest and upper abdomen and whole body FDG-PET or integrated whole body FDG-PET/CT. If clinical suspicion exists, a brain scan (CT or MRI) or a bone scan can be performed.

- 4.3 Randomisation

Recruitment and randomisation will occur when clinical work-up identifies a patient with (suspected) lung cancer in whom further loco-regional staging is indicated. Randomisation will be performed in a 1:1 ratio. Randomisation will occur using a web based program and will be stratified for each participating institution.

- 4.4 Detailed Study Design: flow chart



- 4.5 Inclusion criteria
  - Consecutive patients with known or suspected NSCLC and in whom mediastinal lymph node involvement (either N2 or N3) is suspected based on the available thoracic imaging (CT or CT-PET).
  - Pending the results of mediastinal staging the patient must be considered to be a candidate for surgical resection with an intention to cure.
  - The patient is clinically fit for bronchoscopy, endoscopy and diagnostic surgical procedures.
  - There is no evidence of distant metastatic disease after routine clinical work up
  - The patient is able to give informed consent.
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- 4.6 Exclusion criteria
  - Previous treatment (chemotherapy or radiotherapy or surgery) for lung cancer
  - Any clinical reason why it is thought that the patient is unable to undergo or has a contra-indication to a bronchoscopy, endoscopy, a surgical staging procedure or who is not suitable for definitive surgical resection by thoracotomy.
  - Patients who, based on available thoracic imaging, are unlikely to be staged accurately by any surgical staging procedure (mediastinoscopy/-otomy, VATS).
  - A Concurrent malignancy.
  - An uncorrected coagulopathy.
  - Inability to give informed consent.

Patients who are eligible for this study but who are not included (no informed consent obtained, logistical reasons) will be recorded with the reason why study participation did not occur.

- 4.7 EUS-FNA and EBUS-TBNA (Arm A)

Systematic evaluation of all mediastinal lymph node stations will be undertaken by either EUS-FNA or EBUS-TBNA. Aspirates will be taken of nodes suspected for malignant involvement. It is not in the scope of this study to compare EUS-FNA

and EBUS-TBNA, and thus, it is not necessary to double evaluate those lymph node stations that can be reached by either endoscope (for example LN 7). It is also not in the scope of this study to evaluate the additional value of EBUS-TBNA after EUS-FNA precluding split-echoendoscopy sessions. For reasons of convenience and patient-comfort EUS-FNA will be performed before EBUS-TBNA.

EUS-FNA is performed in a fasting patient as described [21]. Pharyngeal anaesthesia and intravenous conscious sedation will be administered according to local practice. If necessary, prophylaxis for endocarditis will be given according to local institutional practice. If the patient takes oral anticoagulation (warfarin and derivatives or clopidogrel), then this medication should be stopped before the procedure, and proof of normalization of coagulation tests should be available pre-procedure. It is not necessary to stop aspirin or NSAID before this procedure, unless the investigator feels that this is necessary. During the procedure monitoring of pulse rate and oxygen saturation will be performed. EUS will be performed with a linear scanning ultrasound endoscope with Doppler flow imaging for the detection of blood vessels. The EUS endoscope will be introduced into the distal oesophagus, and the investigator will evaluate the mediastinal lymph nodes by scanning 360° transaxially at 1- to 2-cm intervals upwards up to level 2 lymph nodes.

Lymph nodes will be assessed using ultrasonographic criteria for malignancy (short axis diameter, echo-texture, shape, margins, vascular pattern) and suspicious nodes will be biopsied using a 22-guage needle (Echotip®, Wilson-Cook Medical Inc.; Hancke–Vilmann, Winston-Salem, NC or EUS needle, Olympus). Lymph node selection is at the discretion of the operator - it is not within the scope of this study to puncture all lymph nodes. In each patient, lymph nodes suspected of harbouring N3 disease will be sampled first. The presence or absence of direct mediastinal tumour invasion (T4) will also be recorded. If rapid on-site cytopathological evaluation is available it will be utilized although it is not essential within the study. If ROSE is not available suspicious lymph nodes will be sampled a minimum of four times. The number of biopsies per node will be recorded. If necessary, several lymph nodes can be sampled. Samples will be

categorized as positive (tumour cells present), negative (lymphocytes present but no tumor cells), or inconclusive (poor cellularity, or unable to perform adequate biopsy).

EBUS will be performed immediately following EUS. EBUS will be performed with a linear scanning ultrasound bronchoscope (BF-UC160F-OL8, Olympus Ltd) connected to a processor unit (Olympus EU C2000) with Doppler flow imaging for the detection of blood vessels. The bronchoscope will be introduced via the mouth with the patient lying supine and the operator standing behind the patient. Blood vessels will be confirmed using the Doppler mode. Lymph nodes will be evaluated by scanning transaxially at 1- to 2-cm intervals from the peripheral regions of interest (lymph node stations 10-11) upwards to station 2. Lymph nodes will be assessed using ultrasonographic criteria for malignancy (short axis diameter, echo-texture, shape, margins, vascular pattern) and suspicious nodes will be biopsied using a 22-guage needle (EBUS needle NA-201SX-4022, Olympus, Ltd) with a 10-mL syringe for suction. The presence or absence of mediastinal invasion of the primary tumours (T4 or not) will be assessed.

In the event of a patient who is randomised to the test arm being unable to tolerate EBUS/EUS then they will be offered a surgical staging procedure under general anaesthesia. This is in keeping with standard clinical practice. Data will be interpreted on an 'intention to treat' basis for those patients who are randomised.

The mediastinal lymph node map of the American Joint Committee on Cancer will be used to localize abnormalities at CT, FDG-PET or integrated FDG-PET/CT, EUS-FNA, EBUS-TBNA and for mediastinal dissection [22].

- 4.8 Surgical intervention procedures (Arm B)

These include cervical mediastinoscopy, left anterior mediastinotomy or thoracoscopic mediastinal exploration. Surgeons will perform these procedures according to their local institutional practice. However, for cervical mediastinoscopy, the standard of practice requires a systematic sampling of the following lymph node stations: 2R/L, 4R/L and 7 [6].

In the event of mediastinal lymph node evaluation in the EBUS-TBNA/EUS-FNA arm being negative, the patient will proceed to a confirmatory surgical staging procedure prior to a thoracotomy with surgical resection.

At thoracotomy with intra-operative staging, the IASLC guidelines will be followed [23]. This means that a 'systematic lymph node dissection' will be performed for each patient who progresses to a thoracotomy (lobectomy or pneumonectomy). Systematic lymph node dissection is the technique of choice for accurate intraoperative mediastinal staging [24]. It is not mandatory that all mediastinal tissue is removed during intra-operative staging [23].

The following LN stations should be considered:

- Right upper lobe : 2R, 4R and 7
- Right middle lobe : 2R, 4R and 7
- Right lower lobe : 4R, 7, 8 and 9
- Left upper lobe : 4, 5, 6 and 7
- Left lower lobe : 7, 8 and 9

- 4.9 Assessment of lymph node cytology

Lymph node biopsies will be collected and processed by the pathology department according to local protocols. Papanicolau and Giemsa stains will be performed. If sufficient cellular material is available a cell block will be made aiming to complete the cytological analysis of the tumor cells by immunocytochemistry (IHC). The outcome of the cytological analysis will be the presence or absence of malignant cells. The presence of lymphocytes will be regarded as proof of a representative lymph node puncture. A sample of fine needle aspirates obtained by EUS-FNA and EBUS-TBNA will be evaluated by an independent reference cytopathologist in order to assess inter-observer variability. However, the findings of the initial cytopathologist will be used for patient management and the primary analysis. In the event of any dubiety on the part of the pathologist reporting a lymph node biopsy specimen a confirmatory surgical staging

procedure or thoracotomy will be undertaken to ensure that the patient is not in any way disadvantaged by a possible false positive result.

- 4.10 Safety measures and variables

Continuous clinical monitoring and oxygen saturation monitoring during EUS-FNA and EBUS-TBNA procedures will be performed. For all other procedures, routine safety precautions according to local institutional practice will be followed. Any complications of either the EUS-FNA and EBUS-TBNA procedures as well as the surgical procedures will be recorded.

5. Data collection and management

Data collection will be performed in all participating centres. Electronic patient record forms (CRF forms) will be provided in ACCESS. Patient demographics will be recorded. Further recording includes randomisation arm (0=ARM A and 1=ARM B) and randomisation date. All imaging techniques will be recorded (X-ray chest, CT-scan Thorax, CT-scan abdomen, bone scan, FDG-PET/CT scan, brain scan; 0=not done, 1= performed). Following intrathoracic lymph node staging either by EUS-FNA/EBUS-TBNA or surgical staging or both, a cTNM will be noted. Of highest importance, a pTNM will be recorded following each thoracotomy.

Specific EUS/EBUS variables will be recorded. For each lymph node station the presence (1) or absence (0) of enlarged lymph nodes and whether the LN was punctured (0=no, 1=yes), the ultrasonographic characteristics of each LN, the presence of complications (0=no, 1=yes).

Data collection and analysis will be monitored according to good clinical practice. Clinical monitoring will be organised in a cross-over fashion where CRF files will undergo a quality check. Members of each centre will assess some of the files of each other centre. An independent data monitoring and ethics committee and a trial steering group will meet regularly to review the progress of the study and to evaluate the implications of any adverse clinical incidents.

6. Health Economics

A cost-utility analysis from a NHS perspective will be undertaken up to 6 months post-randomisation. Resource use and cost data to be collected prospectively during the study will include resource use associated with the staging and surgical procedures; inpatient length of stay; any adverse events requiring hospital re-admission; and any concomitant oncology treatment (radiotherapy/chemotherapy) that the patients may receive. The outcome measure of interest in the economic evaluation is quality adjusted survival, measured by QALYs (Quality adjusted life years). In order to calculate QALYs, patient utilities will be derived from the EQ-5D questionnaire and combined with patient-specific survival. The EQ-5D questionnaire will be administered to patients at the

following points: a) baseline (at time of randomisation); b) immediately post-staging (EUS/EBUS for group A or surgical staging for group B); c) 3 months post-randomisation; and d) 6-months post-randomisation. The 6-month total mean costs and QALYs will be combined in order to calculate the ICER (incremental cost-effectiveness ratio).

7. Statistical Methods

- 7.1 Sample size and outcomes

In the sample size calculation the following assumptions were made:

The prevalence of mediastinal nodal disease in patients with lung cancer is 70%. The sensitivity of mediastinoscopy to detect mediastinal nodal involvement is 70%. The sensitivity of EUS and EBUS for detection of mediastinal nodal involvement is 90%.

Therefore, using standard calculation techniques, the sample size required is (2 x 71 in each arm) with a power of $1-\beta = 0.8$, type 1 error $\alpha = 0.05$ and two sided testing. Assuming 5% incomplete CRFs and assuming that only 70% of patients will have mediastinal disease the total sample size becomes 214 patients.

For the purposes of statistical analysis, a case of mediastinal disease is defined as a patient with tumour in lymph nodes detected by any of the following: EBUS, EUS, surgical staging techniques or histology following thoracotomy. Thus the 'gold standard' definition is based on a series of tests. Since this definition does not allow for false positive test results, both the specificity and the positive predictive value are necessarily one. Therefore, analysis will focus on the estimation of sensitivity (probability of a positive test in those who have mediastinal disease) and the negative predictive probability (probability of no mediastinal disease in those with a negative test). The negative predictive probability does depend upon the prevalence of mediastinal disease and as discussed above the *a priori* rate of 70% has been assumed for the study population. Formal comparison of the sensitivities will be performed using Fisher's Exact test.

8. Publication and Authorship

Investigators who significantly contribute to the conduct, analysis and publication of the study will be eligible to be a co-author. The study will be registered in the international RCT trial registry.

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